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Childhood Medulloblastoma in Ontario, 1977–1987: Population-Based Results

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A retrospective review was carried out to study children, not more than 16 years old, with a confirmed diagnosis of medulloblastoma, who were residents of the Province of Ontario at the time of diagnosis between 1977 and 1987 inclusive. The provincial tumour registry provided the population database. One hundred and eight children with medulloblastoma were identified of whom 72 (67%) were initially treated at University of Toronto Centres and 36 (33%) at other Health Science Centres, hospitals, and Regional Cancer Centres (RCC) in Ontario. The hospital/Cancer Centre records were reviewed. The 5-year relapse-free survival (RFS) for all patients treated in Ontario was 58% (SE = 5%). Those treated in Toronto had a 5-year RFS of 65% (SE = 6%) compared to 44% (SE = 8%) for those treated in other RCCs in the province ($P = 0.02$). Relapse-free survival for the RCCs ranged from 25 to 60%, with a trend for improved survival with increasing centre size.

Univariate analysis of determinants of relapse-free survival for all 108 patients showed the following variables to be significant: T-stage (Tx + T1 + T2 vs. T3A + T3B) $P = 0.0004$, M-stage (M0+Mx vs. M1–4) $P = 0.0006$, extent of resection (total vs. less than total) $P = 0.002$, radiotherapy (craniospinal irradiation and posterior fossa boost vs. other) $P = 0.02$, and treatment centre (Toronto centres vs. RCC) $P = 0.02$.

Cases treated at centres outside metropolitan Toronto had a nearly two-fold (relative risk = 1.93; 95% confidence interval = 1.07, 3.47) greater risk of recurrence or death than those seen in Toronto. However, in multivariate analysis this difference was not quite significant ($P = 0.07$) after controlling for stage (T and M), extent of resection, meningitis, and gender.

These data suggest that patients with medulloblastoma should be referred for treatment to large centres with major pediatric neurosurgical and oncology resources.

Key words: medulloblastoma, childhood cancer, radiotherapy, prognostic factors

INTRODUCTION

Medulloblastoma is a relatively common paediatric posterior fossa brain tumour. In absolute terms, however, it is rare with an annual incidence of five per million in children under 15 years [1]. The treatment results of 72 children referred to the Hospital for Sick Children (HSC), Toronto have been reported [2]. A preliminary analysis of the population-based data contained in the Ontario Cancer Registry suggested that there was a significant difference in survival between cases treated in Toronto and in the rest of Ontario. Since the Ontario Cancer Registry contains only limited clinical information, a detailed study of all cases diagnosed and treated in Ontario was undertaken.

This report reviews all 108 children, not more than 16 years old, diagnosed with posterior fossa medulloblastoma in the province of Ontario between 1977 and 1987 inclusive, provides population-based provincial outcome data and compares the rates of relapse-free survival for cases seen in Toronto and other regions, and examines whether these differences in outcome can be explained by other prognostic factors.

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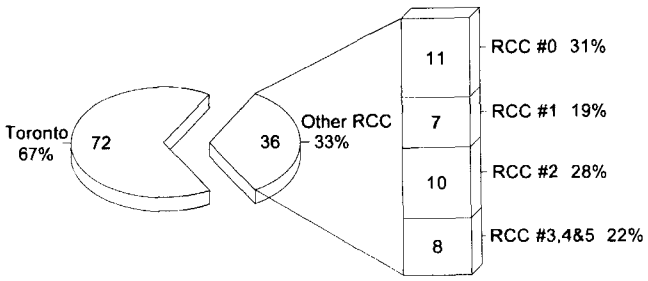

Fig. 1. Distribution of medulloblastoma cases in Ontario between 1977–1987 inclusive by Cancer Centre. Sixty-seven percent were seen at University of Toronto Cancer Centres; 33% were seen at other Regional Cancer Centres. The number of cases seen at each Regional Cancer Centre (RCC 0–5) is shown in the bar diagram.

MATERIALS AND METHODS

In Ontario, which is Canada's largest province (population of 9.1 million at the 1986 census), incident cancer cases are registered by linking hospital discharge summaries, pathology reports, death certificates, and records from specialized cancer centres. The Ontario Cancer Registry identified 108 children with medulloblastoma who resided in Ontario and were diagnosed between 1977 and 1987. All patients were treated, in part, at a cancer centre. This represents an annual incidence of 4.4 cases per million children aged 16 years or less. All cases from the other Regional Cancer Centres (RCCs) were identified and evaluated according to the same criteria used in the Toronto analysis. Elsewhere in the province there were 36 cases of newly diagnosed posterior fossa medulloblastoma in patients not more than 16 years old between 1977 and 1987 inclusive. Data collection was completed in December, 1992 and analysed in early 1993—giving a minimum follow-up of 5 years.

In Ontario, during these years, radiotherapy facilities were centralised to seven RCCs and the Princess Margaret Hospital (PMH). RCCs (1987 annual new patients accrual) are based at University Health Science complexes in Ottawa (3,117), Hamilton (3,729), London (3,315), and Kingston (1,434). Other centres are located in Windsor (1,137), and Thunder Bay (552). At the University of Toronto there are two Cancer Centres, the PMH (6,646) and Toronto Bayview RCC (2,982), which for paediatric malignancy, work in association with the Department of Neurosurgery and Oncology at HSC.

Seventy-two (67%) patients had been referred to The Hospital for Sick Children, Toronto for diagnosis and treatment [2]. Thirty-six (33%) patients had received treatment at one of the six other RCCs in Hamilton, Kingston, London, Ottawa, Thunder Bay, and Windsor and their associated Health Science Centre or hospitals (Fig. 1). Their health records were reviewed. The staging system of Chang et al. [3] was used for retrospective staging. Disease extent was determined from the operative and preoperative Computerized Axial Tomographic Scans reports. All pathology reports were reviewed. The CT scans of patients from RCCs were not reviewed. In the absence of symptoms, cerebrospinal fluid (CSF) positivity and spinal metastases on myelography, the M-stage was assigned as M0, and as Mx when CSF cytology or myelography were not available. The majority of patients from RCCs did not have a CT assessment of the tumour volume after surgical resection, but prior to irradiation. Therefore, the extent of resection was derived solely from the operative note. As in the Toronto series, total resection was defined as complete resection as estimated by the surgeon. Near total resection was defined as 90+% resection, and partial resection as any lesser resection. The RCC data was entered and merged with the Toronto database using Medlog [4].

For surgical and radiation treatment, a similar medulloblastoma treatment policy was followed at all centres. After control of raised intracranial pressure, the tumour was excised, totally if possible, and on recovery craniospinal irradiation was given (3,500 cGy) with a boost to the posterior fossa to raise the dose to the primary site to 5,250–5,500 cGy. Patients with metastatic lesions received additional boost irradiation to the sites of metastasis. However, adjuvant chemotherapy practice was variable.

The relationship between the possible prognostic factors and relapse-free survival was analysed. Relapse-free survival was defined as the interval from the date of surgical resection until relapse, or death if this occurred prior to relapse. Surviving patients who had not relapsed were censored at the date of their last clinic visit (up to December 1992). Nonparametric lifetable methods were used to calculate Kaplan-Meier estimates of survival probabilities, which for patient subgroups were tested for significant differences by the log-rank test [5] and the standard significance level (alpha = 0.05) standard errors for survival probabilities were calculated using Greenwood's formula [6]. Proportional hazards regression models [6] were used to estimate relative risk (RR) and to examine the simultaneous effects of multiple prognostic factors. Relative risk was estimated as the antilogarithm of the regression coefficient for each covariate. For individual parameters in regression models, Wald tests were performed to assess statistical significance. For the treatment centre variable, 95% confidence intervals (95% CI) were estimated. A likelihood ratio test was used to assess whether the treatment centre variable contributed significantly to a multivariable proportional hazards model that contained factors that were found in the univariate analysis to be important indicators of prognosis.

RESULTS

Regional Cancer Centre Cases

The frequencies and univariate analysis of determinants of 5-year relapse-free survival (RFS) grouped by

potential prognostic factors are shown for the 36 Ontario cases seen at RCC outside of Toronto (Table I). The sex distribution was 23 boys and 13 girls (M:F ratio of 1.8). There was a difference in 5-year RFS between the three patients who were younger than 2 years of age, and the 33 patients who were 2 years or older, 0% vs. 48%, but the small number of very young patients made it impractical to assess the significance of this difference.

The retrospective stage assignment was T1 (n = 3); T2 (n = 10); T3A (n = 14); T3B (n = 9); Mx (n = 27); M1–M4 (n = 9). The 5-year RFS for T1+T2 was 69% and for T3A + T3B 30% ($P = 0.04$). None of the nine with M1–M4 were disease-free at 5 years compared to 59% of the 27 Mx cases ($P = 0.0009$).

With increasing T and M stage there is a decrease in 5-year RFS from 100%, for T1, T2, and Mx (n = 9) to 39% for T3A, T3B, and Mx (n = 18) and 0% for any T, M1–M4, (n = 9), ($P = 0.0002$).

From the operative notes, 10 (28%) had a total resection and 26 (72%) had less than a total resection. Extent of resection was significantly associated with RFS, as patients with a total and near total resection had better prognosis than those who had a partial resection or biopsy only ($P = 0.0001$). There were no recorded cases of postoperative meningitis.

Thirteen patients received adjuvant chemotherapy, with the majority (n = 11) receiving a combination of CCNU + Vincristine + Prednisone. Indications for chemotherapy were: age < 2 years (n = 3); stage T3A–T3B (n = 8); and stage M1–M3 (n = 2).

Thirty-five of the 36 patients received post-operative irradiation. One patient, aged 9 months, did not receive post-operative radiotherapy. He had a diagnosis of aqueduct stenosis at age 2.5 months and a shunt was inserted. For this patient, brain CT and CSF were negative, and 7 months later a CT scan showed a posterior fossa mass during investigation for persistent nausea and vomiting. Biopsy confirmed a diagnosis of medulloblastoma. This child died 17 days after biopsy, before radiotherapy was started.

Two patients had palliative cranial irradiation treatment due to their poor general condition. One died 2 weeks after completion of radiotherapy, the other developed spinal recurrence 8 months after his initial treatment and died 4 months later.

The remaining 33 were treated with curative intent, and received craniospinal irradiation. The majority 27/33 (82%) had standard craniospinal irradiation with a boost to the posterior fossa. Two were irradiated to the craniospinal axis with a boost to the whole craniospinal field, and four received craniospinal irradiation with posterior fossa and spine boost. The reason for radiation treatment intensification was the presence of demonstrable metastatic disease. The 5-year RFS for those receiving standard craniospinal and posterior fossa boost was 52% compared to 33% for the six cases with metastases treated by modification of this technique (Table I).

One Centre used a direct moving strip electron field to treat the spinal cord from 1977–1982 and a stationary electron field since 1982. The other five centres used a direct cobalt or 6 MV photon beams to treat the spine.

Of 33 patients treated with curative intent, the craniospinal irradiation (CSI) dose was 2,700–<3,000 cGy for two patients; 3,000–<3,500 cGy for six patients; 3,500–<4,000 cGy for 21, and 4,000–4,500 cGy for five patients. Posterior fossa boost was used in 31 cases and two patients with mets had a boost to the whole C-S axis. The posterior fossa boost dose was equally divided between 500 to <1,000 cGy (n = 10); 1,000–1,500 cGy (n = 10) and >1,500–2,000 cGy (n = 11). The majority received craniospinal irradiation followed by the posterior fossa boost rather than the reverse. The total dose to the posterior fossa was 4,250 (n = 7); 4,500–4,999 (n = 4); 5,000–5,200 (n = 13), and >5,200–<5,700 (n = 7).

Seventeen patients recurred. The site of first relapse was posterior fossa (n = 5), supratentorial (n = 5), systemic (n = 5), spine (n = 2). The majority of recurrences, (n = 16) occurred within the first 3 years after resection. There were no long-term survivors among those who relapsed.

Univariate analysis showed that the majority of variables analysed were not significant predictors of relapse-free survival. Despite the small number of RCC cases, stage, and extent of resection were detected as significant prognostic variables (Table I).

All Ontario Cases

Table II presents results of univariable analyses on all 108 Ontario cases, consisting of the patients included in Table I, plus the previously reported cases from Toronto [2]. Gender, age, period of diagnosis, drain or shunt insertion, meningitis, or adjuvant chemotherapy were not statistically significant predictors of 5-year RFS.

The 108 cases were nearly equally divided between stage Tx + T1 + T2 (50 cases) and T3A + T3B (58 cases) with a 5-year RFS of 77 and 40%, respectively ($P = 0.0004$). The majority of cases were Mx,M0 (84 cases) with a 65% 5-year RFS compared to 31% for the 24 cases who were M1–M4 ($P = 0.0006$). Prognosis worsened with advancing T and/or M stage, from 88% for Tx + T1 + T2 and M0,Mx, to 43% for T3A + T3B and M0,Mx, and 24% for M1–M4 ($P = 0.0001$). There was no patient with stage T4 in our series.

Total resection was achieved in 35% (n = 38) of all cases. Extent of resection was significantly and positively associated with RFS, with 5-year RFS rates of 33% for biopsy, 42% for partial resection, 47% for near total, and 81% for total resection ($P = 0.003$). Meningitis, which was a significant determinant of prognosis in the Toronto

TABLE I. Univariable Analysis of Determinants of Relapse-Free Survival (RFS) in 36 Medulloblastoma Cases From Regional Cancer Centres (Excluding Toronto Cases)*

Variable	No.	5-year RFS rate %	(SE)	Log-rank test (df)	*P*-value
All cases	36	44	(8)	na	na
Period					
1977–1981	17	46	(12)	0.02	0.89
1982–1987	19	42	(11)	(1)	
Sex					
Female	13	54	(14)	0.54	0.46
Male	23	39	(10)	(1)	
Age					
< 2 Years	3	0	(0)	8.84	0.0003
⩾ 2 Years	33	48	(9)	(1)	
Stage T					
T1,T2	13	69	(13)	4.15	0.042
T3A,T3B	23	30	(10)	(1)	
Stage M					
Mx	27	59	(10)	11.09	0.0009
M1–M4	9	0	(0)	(1)	
Stage T and M					
T1,T2, and Mx	9	100	(0)	17.03	0.0002
T3A,T3B, and Mx	18	39	(11)	(2)	
M1–M4	9	0	(0)		
Shunt					
None	12	49	(15)	0.43	0.81
External drain and other shunt	6	33	(19)	(2)	
VP shunt	18	44	(12)		
Total resection					
No	26	42	(10)	0.32	0.57
Yes	10	50	(16)	(1)	
Resection type					
Total	10	50	(16)	21.16	0.0001
Near total	17	52	(12)	(3)	
Partial	8	25	(15)		
Biopsy only	1	0	(0)		
Meningitis					
No	33	45	(9)	na	na
Yes	0	na	(na)		
Chemotherapy					
No	23	39	(10)	0.53	0.47
Yes	13	54	(14)	(1)	
Radiotherapy					
Standard CSI + PF boost	27	52	(10)	3.23	0.19
Intensified boost	6	33	(19)		
Palliative	2	0	(0)		
Centre					
0	11	36	(15)	5.28	0.38
1	7	57	(19)	(5)	
2	10	60	(15)		
3	3	33	(27)		
4	4	25	(22)		
5	1	0	(0)		
Centre size					
Medium (n = 3)	28	50	(10)	1.24	0.27
Small (n = 3)	8	25	(15)	(1)	

*CSI = craniospinal irradiation; df 1 = degrees of freedom; na = not applicable; PF = posterior fossa; SE = standard error; VP = ventriculo peritoneal.

TABLE II. Univariable Analysis of Determinants of Relapse-Free Survival (RFS) for All Medulloblastoma Cases in Ontario (n = 108)*

Variable	No.	5-year RFS rate %	(SE)	Log-rank test (df) and *P*-value	Relative risk estimate	Wald test *P-value*
All cases	108	58	(5)	na	na	na
Period						
1977–1981	55	59	(7)	0.02 (1)	1.0	na
1982–1987	53	56	(7)	$P = 0.89$	1.04	0.89
Sex						
Female	43	70	(7)	3.36 (1)	1.0	na
Male	65	50	(6)	$P = 0.07$	1.78	0.071
Age						
<2 years	14	50	(13)	0.88 (1)	1.0	na
≥2 years	94	59	(5)	$P = 0.35$	0.68	0.35
≤3 years	27	54	(10)			
>3 years	81	60	(6)	$P = 0.34$		
Stage T						
Tx,T1,T2	50	77	(6)	12.77 (1)	1.0	na
T3A,T3B	58	40	(7)	$P = 0.0004$	3.07	0.0007
Stage M						
M0,Mx	84	65	(5)	11.88 (1)	1.0	na
M1-M4	24	31	(10)	$P = 0.0006$	2.78	0.0009
Stage T and M						
Tx,T1,T2, and M0, Mx	41	88	(5)	24.76 (2)	1.0	na
T3A,T3B, and M0,Mx	43	43	(8)	$P = 0.0001$	5.37	0.0003
M1–M4	24	31	(10)		7.96	0.0001
Shunt						
None	42	58	(8)	0.40 (2)	1.0	na
External drain and other shunt	16	46	(13)	$P = 0.82$	1.29	0.56
VP shunt	50	60	(7)		1.01	0.98
Total resection						
No	70	44	(6)	9.87 (1)	1.0	na
Yes	38	81	(6)	$P = 0.002$	0.33	0.003
Resection type						
Total	38	81	(6)	13.96 (3)	1.0	na
Near total	39	47	(9)	$P = 0.003$	2.46	0.026
Partial	28	42	(10)		3.92	0.001
Biopsy	3	33	(27)		6.27	0.019
Meningitis						
No	96	59	(5)	0.30 (1)	1.0	na
Yes	9	51	(18)	$P = 0.58$	1.30	0.58
Chemotherapy						
No	71	59	(6)	0.04 (1)	1.0	na
Yes	37	55	(8)	$P = 0.83$	1.07	0.84
Radiotherapy						
CSI + PF boost	90	63	(5)	5.26 (1)	1.0	na
Other	16	29	(14)	$P = 0.022$	0.44	0.026
Regional centre						
Toronto	72	65	(6)	5.02 (1)	1.0	na
Other	36	44	(8)	$P = 0.025$	1.93	0.028
Centre size						
Large (n = 1)	72	65	(6)	7.42 (2)	1.0	na
Medium (n =3)	28	50	(10)	$P = 0.024$	1.67	0.12
Small (n = 3)	8	25	(15)		3.07	0.014

*CSI = craniospinal irradiation; df = degrees of freedom; na = not applicable; PF = posterior fossa; SE = standard error; VP = ventriculo peritoneal.

series [2], was not statistically significant for all Ontario cases ($P = 0.58$).

Standard craniospinal and posterior fossa boost was used in 63/71 (88%) in Toronto and 27/33 (82%) in other RCC cases. The posterior fossa dose in Toronto was (minimum 43 Gy; maximum 59.5 Gy; mean 51 Gy, SE 0.3) compared to (minimum 42.5 Gy; maximum 57 Gy; mean 49Gy, SE 0.9) for other RCC. Within this narrow

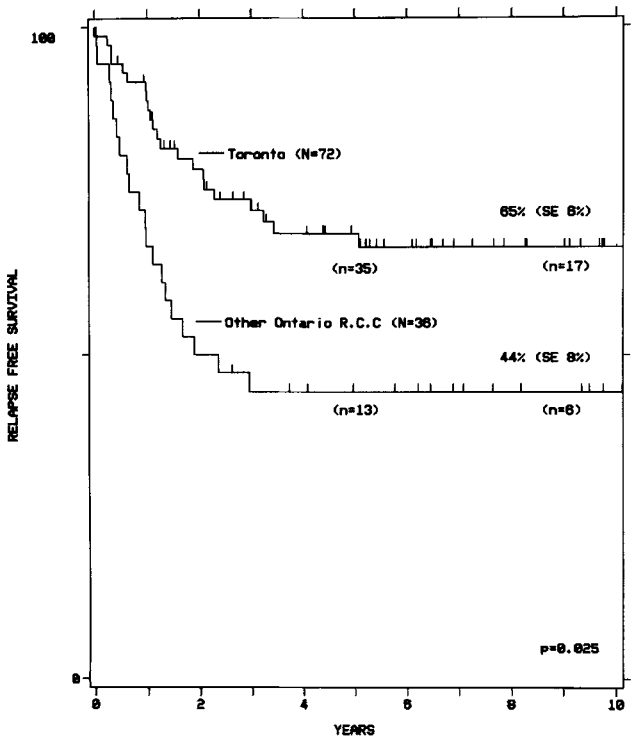

Fig. 2. Relapse-free survival by Regional Cancer Centre (RCC) in Ontario. Tic marks indicate censored cases; (n), number at risk at 5 and 9 years.

range of dose there was no significant difference in relapse rate with doses, between Toronto and other RCC cases. Posterior fossa, as a first site of relapse occurred in 1/14 (7%) for those receiving a total posterior fossa dose of ≤50 Gy compared to 8/76 (10%) for those ≥50 Gy.

The standard craniospinal and posterior fossa boost was used in 85% of cases with a 5-year RFS of 63% compared to 29% for those treated with other irradiation techniques due to the presence of metastatic disease ($P = 0.02$). The other irradiation techniques were CSI only (n = 4), CSI + PF + spine boost (n = 8), CSI + brain (n = 1), and other (n = 3).

Patients treated in Toronto had a 65% 5-year RFS rate compared to 44% for those treated at other Ontario RCCs ($P = 0.02$). There was a 1.93-fold increased risk (95% CI = 1.07, 3.47) among cases seen at other centres, as compared with Toronto. There was a trend towards improved survival with increasing number of cases seen by centre (Table II).

Table III compares the 5-year RFS for medulloblastoma cases at RCCs and Toronto centres by stage and type of radiotherapy. In the Toronto group, M2 and M3 categorisation, that is dissemination to the brain or spinal cord, was confirmed as an adverse prognostic factor, although not at a significant level [2]. The majority of those patients did not have a staging myelogram prior to commencement of radiation therapy. Only 2/15 (13%) of elective myelogram were positive. It was not possible to evaluate the prognostic significance of a positive CSF cytology in that series. In Toronto there were more patients with stage Tx + T1 + T2 and M0,Mx (44%), than in other centres (25%); more complete resection (37%) than in other centres (25%) but an equal proportion with stage M1–M4, (21% vs. 25%). RFS was significantly higher in Toronto cases compared with those from other RCCs for those with stage M1–M4 disease (5-year RFS of 51% vs. 0%, $P = 0.002$), who received any radiotherapy ($P = 0.029$), or who had radiotherapy plus a total resection ($P = 0.05$).

The results of lifetable multiple regression analysis of the relationship between regional cancer centres and disease-free survival, controlling for prognostic factors, among all medulloblastoma cases in Ontario is given in Table IV. Patients with stage M1–M4, have a nearly three-fold risk of relapse compared with those with M0,Mx (RR = 2.63; $P = 0.003$). After controlling for stage (T and M), total resection, meningitis, and sex, the effect of treatment centre (Toronto vs. other RCC) was less significant ($P = 0.07$) than initially observed in univariate analyses ($P = 0.03$), although the relative risk estimate (1.85; 95% CI = 0.97, 3.65) indicated that the risk of recurrence or death was 1.85 times (or 85%) greater among cases seen at other RCCs.

DISCUSSION

The population-based 58% five-year RFS for the 108 medulloblastoma patients treated in Ontario is similar to recent results reported in the literature. Those treated in Toronto had a 5-year RFS of 65%, compared to 44% for those treated in other RCCs in the province. Relapse-free survival for the RCCs ranged from 25 to 60% (Fig. 2), with a trend for improved survival with increasing centre size.

This article examined whether the difference in survival between patients treated in Toronto and other Ontario RCCs was due to differences in the distribution of prognostic variables and treatment programs. Other factors which could also influence survival rates, but could not be evaluated in this study, include differences in regional expertise and resources.

For medulloblastoma, previous reports [7–9] have shown that the extent of surgical resection and the use of craniospinal radiation in sufficient doses was associated with an improved survival.

Treatment modalities were similar in Toronto and RCC series. Extent of resection was a significant prognostic variable ($P = 0.002$), in both the Toronto and RCCs series. The difference was most marked for total against less than total resection for Toronto, compared to total and near total against less than near total for RCCs.

TABLE III. A Comparison of Relapse-Free Survival (RFS) for Medulloblastoma Cases at Regional and Toronto Centres, by Stage and Type of Radiotherapy†

	Regional centres			Toronto centres			
		5-year RFS rate			5-year RFS rate		Log-rank test
Variable	No.	%	(SE)	No.	%	(SE)	and *P*-value*
Stage T and M							
Tx,T1,T2, and M0,Mx	9	100	(0)	32	83	(7)	1.78, $P = 0.182$
T3A,T3B, and M0,Mx	18	39	(11)	25	46	(11)	0.72, $P = 0.40$
M1–M4	9	0	(0)	15	51	(14)	9.75, $P = 0.002$
Any radiotherapy	35	46	(8)	71	66	(6)	4.77, $P = 0.029$
CSI + PF boost	27	52	(10)	63	68	(6)	2.37, $P = 0.123$
CSI + PF boost plus total resection	8	63	(17)	27	93	(5)	3.70, $P = 0.054$
Less than total resection	19	47	(11)	36	48	(9)	0.14, $P = 0.71$

†CSI = craniospinal irradiation; PF = posterior fossa; SE = standard error.
*All log-rank tests are on one degree of freedom.

TABLE IV. Multivariable Analysis of the Relationship Between Use of Regional Treatment Centres and Relapse-Free Survival, Controlling for Prognostic Factors, Among Medulloblastoma Cases in Ontario

Variable	Relative risk	Wald test *P*-value	Likelihood ratio test*
Stage T			
Tx,T1,T2	1.0	na	na
T3A,T3B	1.74	0.16	
Stage M			
M0,Mx	1.0	na	na
M1–M4	2.63	0.003	
Total resection			
No	1.0	na	na
Yes	0.53	0.15	
Meningitis			
No	1.0	na	na
Yes	1.88	0.21	
Sex			
Female	1.0	na	na
Male	1.44	0.27	
RCC			
Toronto	1.0		3.38 (1 df)
Other	1.85	0.063	$P = 0.066$

*Likelihood ratio test for addition of Regional Cancer Centres (RCC) variable to multivariable model, showing degrees of freedom (df) and level of significance (*P*).

This could be due to differences in interpretation of the definition of extent of resection by individual surgeons. In the Toronto series, near total resection was defined as ≥90% resection. It was not possible to obtain a CT assessment of post-resection, pre-irradiation tumour volume in the patients from other RCCs, so that the extent of resection was derived entirely from the operative note.

There was a tendency for more patients in Toronto to have complete resection (39%) compared to 28% for other RCCs. Albright et al. [10] reviewed the neurosurgical reports of children with posterior fossa medulloblastoma treated in two CCSG protocols and showed that "near total" and "gross total" resection were performed significantly more often ($P < 0.05$) by paediatric neurosurgeons than by general neurosurgeons with no significant differences in patient morbidity between the two groups. Whether the difference between Toronto and RCC patients is due to better facilities, differences in definition of complete resection, or surgical expertise is impossible to evaluate from this study.

Adjuvant chemotherapy was used in (33%) of Toronto and (36%) of RCC cases. The fact that survival was not significantly affected by chemotherapy may have occurred because patients with unfavourable prognostic features were selected for chemotherapy.

Radiotherapy plays a major role in the treatment of

medulloblastoma. The technique for craniospinal and posterior fossa boost irradiation has been well described in several reports [11,12]. The radiotherapy technique and doses used were similar across the regional centres and were comparable to those used in Toronto.

Five year RFS for Toronto and Regional centres by stage and radiotherapy technique is shown in Table III. There was a difference in 5-year RFS for all cases treated by irradiation between Toronto and RCC ($P = 0.03$). The majority, 27/33 (82%) of RCC cases and 63/71 (88%) Toronto cases, were treated with curative intent by standard craniospinal and posterior fossa boost. There was no statistical difference in their 5-year RFS, 52 and 68%, respectively ($P = 0.12$). When only those who received craniospinal and posterior fossa boost irradiation are considered, there is a significant difference ($P = 0.05$) for those who had a total resection, but not for those with less than a total resection ($P = 0.71$).

A recent report from London (Ontario) [13] showed a 5-year survival of 57% for all 32 cases of paediatric and adult medulloblastoma treated between 1968 and 1986. The radiotherapy technique used in London differs from that used in other centres, in that the spinal field is treated with an electron beam. An analysis of their results concluded that electron spinal field irradiation gave results comparable to those in the literature. The technique and dose used in the rest of the province is very similar to that in Toronto.

Local expertise and treatment variations could account for the observed difference. Patient positioning and field matching are critical in craniospinal irradiation. "Underdosed" areas in the CNS, for example the cribriform plate due to generous shielding of the eyes, are high-risk sites for tumour recurrence [14–16]. A recent review of quality control of radiotherapy treatment of medulloblastoma in a multicentre study showed that in 10 of 22 patients with relapses, treatment failure was probably due to a radiotherapy protocol variation [17]. The effect of radiotherapy treatment variations between the Toronto and other RCCs cannot be determined without a more detailed review of radiotherapy technique and dose. The pattern of relapse between the Toronto and other RCCs were similar and did not suggest this as an important factor.

Among the prognostic variables analysed, post-operative meningitis was important in Toronto. Since meningitis, in the Toronto analysis, had a negative effect on survival, it would tend to mask the survival difference between the two groups.

Univariate analysis (Table II) showed treatment centre (RCC vs. Toronto $P = 0.02$), extent of resection (total vs. less than total $P = 0.002$), stage (M1–4 vs. M0–Mx $P = 0.0006$; Tx + T1 + T2 vs. T3A + T3B $P = 0.0004$) as statistically significant variables. Cases treated at centres outside metropolitan Toronto had a two-fold (RR = 1.9) greater risk of recurrence or death than those seen in Toronto. However, after controlling for stage, extent of resection, post-operative meningitis and gender, treatment centre was not a statistically significant prognostic factor ($P = 0.07$ in Table IV), although the relative risk estimate (RR = 1.85) was only slightly lower than in the univariable analysis.

Our analysis indicates that in Ontario, all Cancer Centres have a similar management approach for medulloblastoma. Treatment centre is not as significant a prognostic variable as initially suspected. Some of the factors which could have accounted for the trend towards better survival with centre size, namely access to CT, MRI scans, and paediatric neurosurgeons may no longer apply to RCCs based at University Health Science complexes. On the other hand, these results suggest that risk was slightly elevated among cases seen at centres other than Toronto. The confidence interval for the treatment centre variable from the multivariable analysis (relative risk = 1.85 95% CI = 0.97, 3.55), indicated that the true value of the relative risk probably ranged from slightly less than one, up to a 3.5-fold increased risk. The width of the confidence interval indicates that despite the fact that this was a population-based study, it still had somewhat limited statistical power. To distinguish the small levels of detected relative risk from chance variation, studies of larger population would be required.

For relatively rare diseases, such as medulloblastoma, which require complex treatment, a minimal number of cases should be seen to ensure optimal expertise. This review suggests that referral of those patients by smaller centres to larger ones should further improve the excellent results achieved in Ontario.

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